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February 11, 1999

BY HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

Re: Comments to Docket No. 98N-0148

To Whom It May Concern:

Hyman, Phelps & McNamara, P.C. respectfully submits these comments to Docket No. 98N-0148. Please note that we mailed copies of these comments to the Dockets Management Branch last night to take advantage of FDA's postmark rule, 21 C.F.R. § 10.20(e). The attached certified mail receipt indicates that these materials were postmarked on February 10, 1999. Accordingly, please enter these comments into the FDA Log as received on February 10, 1999.

Respectfully submitted,

Eric Rogers

EER/tee
Attachment

98N-0148

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99 FEB 11 P1:50

February 10, 1999

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

Re: Notice Titled "International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization Scheduling Recommendation for Ephedrine, Dihydroetorphine, Remifentanil, and Certain Isomers;" Docket No. 98N-0148

To Whom It May Concern:

Hyman, Phelps & McNamara, P.C. submits these comments on behalf of clients who manufacture dietary supplements containing extracts of the herb Ephedra. The comments are in response to the above-referenced notice of the World Health Organization ("WHO") recommendation to the United Nations Commission on Narcotic Drugs ("CND") to add ephedrine to Schedule IV under the 1971 Convention on Psychotropic Substances ("1971 Convention"). Based on the lack of any measurable data that ephedrine has been abused in a manner to warrant scheduling, we request that the Food and Drug Administration ("FDA") and U.S. Delegation to the CND take immediate action to either oppose the scheduling of ephedrine under the 1971 Convention, or have the scheduling vote deferred.

As established in these comments, FDA must not wait to act until after the public hearing scheduled on February 19, 1999, but must act now to avoid scheduling. Otherwise, scheduling might occur regardless of FDA's and the U.S. Delegation's opposition. The unwarranted scheduling of ephedrine will place continued international cooperation in the drug control effort at serious risk.

I. Introduction.

A large number of dietary supplement manufacturers in the United States sell dietary supplements containing extracts of the herb Ephedra, supplements that contain small amounts of ephedrine and related ephedrine alkaloids. They are widely and safely consumed in the United States and in other countries for weight management and other purposes. These supplements are sold via several traditional retail channels, including drug stores, health food stores, mass-merchandise retail stores, shopping malls, and mail-order catalogs. Many companies also distribute dietary supplements through direct sales distribution.

Two of these direct sales companies alone have over 200,000 independent distributors. The total number of independent distributors in the direct sales of supplements that contain Ephedra extracts is estimated to exceed 500,000. Many of these distributors depend on income from sales of these products to supplement their household income.

Supplements containing Ephedra extracts are among the more popular products in a rapidly expanding industry. Conservatively, annual sales of these supplements are estimated to be in the $500 to $900 million range.

Millions of individuals consume dietary supplements containing Ephedra extracts and over-the-counter ("OTC") drug products containing ephedrine. The statement of a recognized expert on drug abuse, Dr. Edgar Adams, is included with these comments. As his analysis shows, despite FDA's comments to the contrary, there is no evidence in the United States or in other countries of measurable abuse of these products. There is also no indication that use of dietary supplements containing Ephedra extracts will lead to addiction or cause public health or social problems. Consequently, there is no basis to control ephedrine as a Schedule IV drug either internationally or domestically.

Scheduling of ephedrine and application of the prescription requirements of such scheduling will have the unacceptable effect of nullifying important U.S. laws, including the Chemical Diversion Control Act of 1988, the Domestic Chemicals and Diversion Control Act of 1993, the Comprehensive Methamphetamine Control Act of 1996, as well as important provisions of the Dietary Supplement Health and Education Act of 1994. Such scheduling would also circumvent three important pending rulemaking proceedings, FDA's July 27, 1995 proposed rule on ephedrine-containing OTC drugs, 60 Fed. Reg. 38,643, FDA's June 4, 1997 proposed rule on dietary supplements containing ephedrine alkaloids, 62 Fed. Reg. 30,678, and the Drug Enforcement Administration's ("DEA's") September 16, 1998 proposed rule on chemical mixtures, 63 Fed. Reg. 49,506. If prescription status was required as a result of international scheduling of ephedrine, all of these pending rulemakings would become irrelevant, thereby circumventing the due process controls that are afforded the public and industry under the laws of the United States.

Finally, there are serious problems with the process that has been used to bring the issue of scheduling ephedrine to a vote in March. The WHO review of ephedrine has resulted in the misinterpretation and distortion of data, and because WHO has ignored its own procedures there has been no meaningful opportunity for public input into the process to correct these errors. As a result, apparently for purely political reasons, WHO has recommended scheduling of a substance, ephedrine, that all qualified drug abuse experts would agree is not an abused substance, and that therefore cannot be scheduled under the 1971 Convention.

Even though FDA received notice of the WHO scheduling recommendation on November 11, 1998, FDA did not publish a notice in the Federal Register until January 11, 1999. The CND vote is scheduled for March, and FDA has the task of considering comments, holding a hearing, and making a recommendation to the United States Delegation based on all of the information provided. The WHO schedule and FDA's delay has left industry with less than one month to file comments on an issue of monumental importance to the public and the economy. **Under any standard, it is obvious that the WHO and FDA "process" is a charade, and that there will not be sufficient time for the information that is submitted to FDA to be given thorough consideration.**

If scheduling of ephedrine occurs and dietary supplements and OTC drugs are forced off the market through a requirement for prescription sales, a precedent will be set that the United States and other member countries will not tolerate. Scheduling, which would likely require that all ephedrine products be distributed by prescription, would have an enormous impact on the availability of safe and cost effective products such as dietary supplements and OTC drugs. Prescription status would almost certainly eliminate the market for these products, having an effect on the U.S. economy of several billion dollars. Further, the elimination of these safe and useful products would have a negative impact on consumer health and the cost of health care. Dr. Adams and other drug abuse experts agree that there is no evidence of abuse of ephedrine. Therefore, the CND may not place ephedrine under international control. See 1971 Convention, art. 2, para. 4. If ephedrine is allowed to be scheduled for political reasons, the end result will be to cause a serious erosion of the international drug control effort, an effort that the United States has historically helped to lead. Funding for continued international drug control efforts will be put in jeopardy.

It is now FDA's obligation to make certain that this unfair and ill-considered process comes to a rapid end. FDA must not wait for the public meeting on February 19, 1999, but must notify the U.S. Department of State ("State Department") of the problems that scheduling will cause, and to urge the State Department to take whatever action is necessary to immediately cancel or defer the CND vote that is scheduled to take place in March.

II. The Evidence of Ephedrine Misuse or Abuse in the United States or Other Countries Does Not Support International Scheduling.

Under the 1971 Convention, WHO can recommend to CND the international scheduling of a substance only if it finds: (1) that a substance is capable of producing dependence and is a central nervous system ("CNS") stimulant or depressant, or has similar abuse potential to a current Schedule I, II, III or IV drug; and (2) there is sufficient information of abuse or potential abuse to "constitute a public health and social problem warranting . . . international control." 1971 Convention, art. 2, para. 4. The current scientific, medical and epidemiological evidence both in the United States and the international community does not support scheduling ephedrine under the criteria of the 1971 Convention. In fact, the data in the United States and in other countries are consistent, and they prove a lack of measurable abuse of ephedrine in any form, particularly in relation to the wide availability of products containing this substance.

The following review and analysis of the data on possible abuse of ephedrine is based on the comments of Dr. Edgar H. Adams, an expert in the study of drug abuse. Dr. Adams worked for 19 years with the National Institute of Drug Abuse (NIDA), and was Director of NIDA's Division of Epidemiology and Statistical Analysis. In this position he supervised the Drug Abuse Warning Network (DAWN) and other drug abuse data collection programs. See Adams Statement ¶ 1. (Included as Appendix A.)

A. The U.S. Data Provided to WHO by FDA Does Not Indicate Abuse of Ephedrine.

There is no evidence that ephedrine "is being or is likely to be abused so as to constitute a public health and social problem" in the United States – or elsewhere – and thus, there is no basis for WHO's recommendation that ephedrine be classified in Schedule IV under international treaties. See Adams Statement ¶ 3. A review of the information that FDA provided to WHO as part of the critical review on ephedrine confirms this fact.

In response to the WHO inquiry on the extent of abuse of ephedrine, FDA cited data from the Drug Abuse Warning Network ("DAWN") from 1994 to 1996. See FDA Response at 1-2 (included as Appendix B). The DAWN data clearly indicate however, that ephedrine is not being abused in the United States. DAWN data from 1989 to 1996 show that ephedrine episodes represent less than half of one percent of the total in any given year. See Adams Statement ¶ 12. The number of emergency room mentions for 1994 (2363 mentions) is a materially small number compared to other drugs annually reported in DAWN. This is true even when comparing ephedrine mentions to other OTC drug products (e.g., 38,674 episodes for acetaminophen and 19,358 for aspirin). See Adams Statement ¶ 11.

There is also a strong indication that even this small number of ephedrine abuse episodes is inflated. First, it is likely that some of the ephedrine mentions are related to suicide attempts or gestures because these incidents are reported in DAWN. In fact, six of the top thirty drugs, representing almost one fifth of the mentions in DAWN, are OTC drug products, mostly because of "medicine cabinet" suicide attempts or gestures that are reported to DAWN. See Adams Statement ¶ 12. These cases should be excluded when considering the evidence to support drug abuse policy. Id.

Second, the methodology used to report DAWN data has changed since 1989, and the use of weighted data has caused fluctuations in the data that in the case of ephedrine should be taken into consideration. For example, in 1989 there were only 66 actual reported episodes involving ephedrine but the weighted episodes for that year were reported as 441. Therefore, the actual number of abuse cases of ephedrine reported in DAWN may be even smaller than currently reported. See Adams Statement ¶ 13. FDA referenced two reporting sources in response to WHO's inquiry as to the "degree of seriousness of the public health and social problems" from ephedrine abuse. See FDA Response at 2. FDA referred to the agency's Spontaneous Reporting System ("SRS"), which only identified 35 cases of possible ephedrine misuse or abuse over a 15-year period from 1983 to 1997. Most of these reports indicate that multiple substances were involved with no delineation of whether ephedrine was being abused. At least eight and probably more of the reports involved suicide attempts or gestures, and six had blood alcohol levels ranging from 0.06 to 0.19 percent. Considering the widespread consumption of products containing ephedrine, these reports do not provide any measurable indication of a serious health problem from ephedrine abuse. See Adams Statement ¶ 14.

The second source cited by FDA in response to WHO's question concerning the "seriousness" of ephedrine abuse was the data provided by the Texas Department of Health ("TDH"). As with the DAWN and SRS data, the TDH data are inconclusive and simply do not indicate a problem of abuse of dietary supplements containing Ephedra extracts. See Adams Statement ¶ 15. For example, of the 193 cases reported, there was only one case that could be attributed to a dietary supplement. See TDH Comment, FDA Docket No. 98N-0148, cmt. 9, att. 1, at 11 (entry for "Ma Huang").

In response to WHO's question of the number of seizures of ephedrine in illicit trafficking during the past three years, FDA cites to DEA's System to Retrieve Information and Documentary Evidence ("STRIDE"). FDA acknowledges, however, that most of these seizures relate to diversion of ephedrine in the illicit manufacture of methamphetamine, and not abuse of ephedrine. FDA speculates that some of the seizures "may" be associated with ephedrine abuse. Approximately 300 cases involved seizures of less than 200 tablets. However, there is no evidence that these cases involved abuse of dietary supplements containing Ephedra extracts or OTC drug products, and this statement ignores the fact that DEA has reported a dramatic increase in small "mom and pop" clandestine laboratories

making very small amounts of methamphetamine. See Adams Statement ¶ 17. In this context, seizures of small quantities of ephedrine in clandestine laboratories is entirely consistent with the illicit manufacture of methamphetamine. In contrast, there is no basis to interpret these data as evidence of "abuse."

FDA also provided information to WHO on the U.S. distribution of illegal drugs mislabeled as dietary supplements and marketed as MDMA "look alike" drugs, such as Herbal Ecstasy and Ultimate Xphoria in the United States. See Adams Statement ¶ 20. However, FDA failed to point out to WHO that the agency has addressed the marketing of these illegal drugs by issuing warning letters to companies that market these products. See FDA Warning Letters (included as Appendix C). The warning letters, which state that FDA will pursue civil and/or criminal action for failure to remove these products from the market place, is an effective and appropriate remedy to this problem. Scheduling ephedrine is inappropriate and will have no impact on the marketing of these already illegal products. See Adams Statement ¶ 20.

Finally, FDA acknowledges that the U.S. government has no evidence of clandestine laboratories manufacturing ephedrine. See FDA Response at 6. This is a significant indicator that ephedrine is not being misused as a substance of abuse. See Adams Statement ¶ 17. FDA did provide information to WHO on the problem of diversion of ephedrine to make methamphetamine and correctly notes that Congress has passed three Federal laws to reduce the diversion and trafficking in ephedrine and other substances. These laws are consistent with the U.S. obligation under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 ("1988 Convention").

As Dr. Adams succinctly concluded, "there is virtually no information that indicates that dietary supplements that contain small amounts of ephedrine alkaloids or OTC drug products are being abused." Adams Statement ¶ 8.

B. The WHO Critical Review Document Does Not Provide a Basis for Scheduling Ephedrine.

The WHO Critical Review Document addresses a number of subject areas related to ephedrine including the pharmacology, pharmacokinetics, dependence potential, (preclinical and clinical studies) epidemiology of use and abuse, nature and magnitude of public health problems and national control. See WHO Critical Review at 2-10 (included as Appendix D). The review notes that ephedrine is both an alpha and a beta agonist and enhances the release of norepinephrine from sympathetic neurons. It further states that "ephedrine is viewed as being a less potent CNS agent but a more effective bronchodilator." Id. at 3. That ephedrine is a weak CNS stimulant is confirmed in preclinical and clinical studies.

The evidence presented in the critical review does not meet the criteria for recommending scheduling. WHO has not shown that ephedrine may cause dependence, that ephedrine is abused as a CNS stimulant (or is subject to a similar level of abuse as a currently scheduled drug), and that ephedrine abuse is potentially a public health or social problem. See 1971 Convention art. 2, para. 4. "At best, the evidence of dependence cited in the WHO critical review document demonstrates that ephedrine has mild stimulant properties." Adams Statement ¶ 19. There is absolutely no evidence to even suggest, however, that ephedrine may lead to dependence or that use of ephedrine constitutes a public health or social problem.

The responses to the WHO request for information provided by other nations demonstrate that there is little evidence of abuse of ephedrine and, more important, no real demand for scheduling of ephedrine. See Adams Statement ¶ 21. WHO stated that it sent a questionnaire to 191 countries, of which 50 countries responded. See WHO Critical Review at 8. Of these 50 countries, only 4 do not allow the medical use of ephedrine. Of these 4, only 1 country (Sudan) indicated that it banned the use of ephedrine due to past problems of abuse.

In the 46 countries that authorize medical use of ephedrine, only 11 provided information on very limited past or present problems of abuse. See WHO Critical Review at 9. China and Germany indicated that there is no current abuse problem, which is especially significant when one considers that China is one of the largest exporters of ephedrine raw material. Belgium, Finland, France, Slovakia, and Thailand indicated that abuse was limited to "a few cases." Ireland reported abuse of ephedrine only in relation to misuse as an MDMA "look alike." Burkina Faso reported seizures of ephedrine but did not identify an abuse problem per se. Finally, Costa Rica indicated that ephedrine is abused as a "doping agent," but did not further explain the problem. The information on abuse provided by the United States is described in Section II.A., above.

Viewing the country responses in another way, only 27 of the 46 countries that allow the medical use of ephedrine reported some form of distribution control. See WHO Critical Review at 11. Of these 27, 14 allow at least some ephedrine preparations to be sold over the counter. The 14 countries that allow OTC distribution include 3 countries that identified some form of limited past or present abuse problem. Thus, the data demonstrate that, even in countries where ephedrine is available OTC, there is little or no abuse problem present. See Adams Statement ¶ 23.

The WHO scheduling recommendation twice observed that "[t]he problem of abuse seems to be particularly serious in certain African countries." 64 Fed. Reg. 1629, 1630 (Jan. 11, 1999). The available evidence – including a document distributed at the WHO scheduling meeting – do not, however, indicate a significant problem of abuse. In a document entitled "Background Paper for Dr. Cortes-Maramba," the evidence of abuse was

limited to International Narcotics Control Board's ("INCB's") observations for 1996 and 1997 that "[t]he quantities of ephedrine imported by some African States seems very large compared with the quantities imported by other States," and that "the quantities of ephedrine imported by some African States seemed to be excessive." See Background Paper at 3 (emphases added) (included as Appendix E). The background paper also identified nine cases of attempted diversion of varying quantities of ephedrine and ephedrine tablets from 1989 to 1998. The available evidence does not establish that any "abuse" has occurred, let alone show that there is a pattern of "particularly serious" abuse. See Adams Statement ¶ 24. Without further study, it is impossible to determine whether the "seemingly excessive" African imports are subsequently abused in the importing countries.

Ephedrine also fails to meet the criteria for scheduling when compared to other drugs already scheduled under either the 1971 Convention or U.S. law. Even a cursory review of the drugs in Schedule IV of the convention, e.g., benzodiazepines, demonstrate the fallacy in the current WHO recommendation. See Adams Statement ¶ 7. Substances such as codeine, benzodiazepines, and barbiturates are subject to control based on significant scientific, medical and epidemiological data of abuse and potential for dependence. The lack of such data for ephedrine makes its scheduling under the 1971 Convention entirely inappropriate.

III. FDA's Submission to WHO Caused Confusion and Ultimately Misrepresented the Evidence of Abuse in the United States.

The 1971 Convention requires WHO to notify the parties to the convention whenever it plans to consider the addition of a substance to one of the international schedules. See 1971 Convention, art. 2, para. 1. The CSA subsequently requires FDA to publish the WHO notification in the Federal Register in order to "provide [an] opportunity to interested persons to submit . . . comments respecting the scientific and medical evaluations" necessary in formulating "such medical and scientific evaluations as may be appropriate" to respond to the WHO notification. CSA § 201(d)(2)(A), 21 U.S.C. § 811(d)(2)(A) (emphasis added). In this case, FDA's response was far from "appropriate," however, as the agency provided a large volume of extraneous material and information that caused confusion at WHO about the available scientific data on ephedrine abuse.

A. FDA's June 4, 1997 Notice of Proposed Rulemaking Focused on Product Safety, Not Abuse, and Should Not Have Been Submitted to WHO.

FDA submitted a copy of the June 4, 1997 proposal to regulate dietary supplements containing ephedrine alkaloids as a partial answer to WHO's question regarding the availability of ephedrine. The proposed regulation, which is still pending, would establish various daily intake and labeling restrictions for dietary supplements containing Ephedra extracts. See 62 Fed. Reg. at 30,678. The proposed rule is based on a collection of adverse

event reports ("AERs") that FDA alleges demonstrate safety issues concerning these dietary supplements. See id. at 30,679. The proposed rule focuses entirely on safety, not abuse.

The only information that might be interpreted as dietary supplement "abuse" in the proposed rule is limited to one part of one sentence in a 47-page proposal. See 62 Fed. Reg. at 30,679. That portion of the Federal Register notice implies that dietary supplements may legally be marketed for "euphoria or as alternatives to street drugs." Id. This is incorrect, as is made clear by FDA's own warning letters that have been sent to manufacturers of these illegal products. These products are illegal drugs, not legal dietary supplements.

It is not clear why FDA submitted a Federal Register notice of proposed rulemaking that contained 47 pages of extraneous material. The volume of extraneous information in this one document is astounding given the three columns of small print on each page. To WHO, this document must have been imposing indeed. FDA should have foreseen the ultimate effect of such a submission, that WHO would misinterpret the proposed rule and misapply the information. That is in fact what occurred.

B. By Presenting the Remainder of the Government Data out of Context, FDA Further Confused WHO Concerning the Scope of Abuse in the United States.

As described in Section II I.A. above, FDA did not provide sufficient evidence of ephedrine abuse to warrant scheduling under U.S. law or the international schedules. However, by linking several data sources together, even ones lacking substance, FDA made it appear that the United States had identified a significant problem of ephedrine abuse. In its letter to WHO, FDA cited to four data sources (DAWN, SRS, STRIDE, TDH) in addition to its proposed rule on dietary supplements. This implied that the United States was tracking abuse of ephedrine on multiple levels when in fact the data indicated that ephedrine was not being abused on any level. In addition, FDA's reference to diversion of ephedrine for illicit manufacture of methamphetamine added to the confusion. FDA presented the diversion of ephedrine as if it were data to support scheduling, without any proof of abuse.

IV. Not Surprisingly, WHO Misinterpreted the Data FDA Submitted.

The WHO Critical Review Document contains several statements that either misconstrue the data submitted by FDA or are plainly wrong. In a section entitled "Epidemiology of Use and Abuse with an Estimate of the Abuse Potential," WHO stated that the "DAWN data indicate an increase in drug abuse episodes of ephedrine and pseudoephedrine." WHO Critical Review at 9. In its response to the WHO questionnaire, FDA presented the following DAWN data:

Year	DAWN ER Ephedrine Mentions	DAWN Medical Examiner Mentions
1994	2363	30
1995*	1880	20
1996*	2420	NA

* Estimates for 1995 and 1996 are preliminary.

See FDA Response at 1. Even ignoring the substantive problems with FDA's presentation of the data, the DAWN data simply do not indicate any trends whatsoever. See Adams Statement ¶¶ 11-13.

WHO also referenced the STRIDE data, which FDA should never have cited in the first place, as evidence of abuse in the United States, stating that that the "STRIDE data for the 6-year period 1992-1997 indicated . . . about 300 cases[ ] were likely to have been associated with ephedrine abuse." WHO Critical Review at 9 (emphasis added). The FDA submission, by comparison, identified approximately 300 cases that "may be associated with ephedrine abuse," and further noted that "this is not confirmed." FDA Response at 2 (emphasis in original). Dr. Adams establishes that even FDA's speculative statement is without any foundation. See Adams Statement ¶ 17.

WHO also stated that "[a]dverse events tabulated for ephedrine products sold as food supplements for the State of Texas were reported by the Centers for Disease Control (CDC)." WHO Critical Review at 9. This statement is wrong on two counts. First, the Texas data nearly exclusively relate to a problem with a single ephedrine OTC drug product, which has been reformulated to address the abuse issue - out of 193 database entries, only a single entry pertains to Ephedra dietary supplements, and that entry lacks attribution. See TDH Comments, FDA Docket 98N-0148, cmt. 9, att. 1, at 11 (entry for "Ma Huang"). The WHO critical review document reference to "food supplements" is in error.

Second, WHO erroneously stated that the Texas data derive from the Centers for Disease Control ("CDC"), the internationally recognized research arm of the Department of Health and Human Services. As FDA's submission to WHO makes clear, the data were compiled by TDH from telephone calls placed to various Texas poison control centers. See FDA Response at E83. The Texas data are in no way related to the CDC. Most, if not all, of the WHO members are aware of the international reputation of the CDC, and would likely be inclined to give weight to CDC findings. The Texas data do not deserve to be

pictured as supported by CDC, and readers of WHO's report responsible for recommending scheduling of ephedrine have been substantially misled.

Finally, the WHO Critical Review Document states that "[i]n the USA, the abuse of dietary supplements containing Ma Huang prompted the FDA to set threshold levels of ephedrine ingestion through the use of Ma Huang." WHO Critical Review at 10. This statement is a reference to FDA's June 4, 1997 notice of proposed rulemaking. As noted previously, however, the AER data contained in the preamble to that proposed rule apply only to alleged safety issues – the notice does not focus on or contain allegations of dietary supplement abuse. Further, WHO has not surprisingly failed to recognize that FDA has proposed limits, not "set" limits as WHO states. By repeating FDA's inappropriate safety allegations, WHO amplified the confusion with respect to the differences between safety and abuse. WHO has made it appear that FDA has acted to limit abuse of these legal products. Again, readers of WHO's report responsible for the scheduling decision were misled.

FDA presented WHO with a large volume of misleading information. The group responsible for preparing the WHO Critical Review Document misinterpreted and mischaracterized the evidence of U.S. ephedrine abuse to the ECDD committee members. FDA must now accept responsibility for the mistakes, and must take whatever action is necessary to make certain that international scheduling of ephedrine does not occur.

V. International Scheduling of Two Ephedrine Isomers Will Create Jurisdictional Conflicts Between the 1971 and 1988 Conventions.

The 1988 Convention established controls over precursor chemicals, including ephedrine, to prevent diversion and misuse of these products. WHO's recommendation to schedule two ephedrine isomers under the 1971 Convention is impracticable and will create a jurisdictional conflict in administration of international drug control.

A. International Scheduling of Only Two Ephedrine Isomers Is Impracticable.

WHO has proposed to schedule one stereoisomer of ephedrine (*l*-ephedrine) and its racemate (*d,l*-ephedrine), however there is another stereoisomer of ephedrine (*d*-ephedrine). This action is impracticable in that the current regulation and reporting of ephedrine does not distinguish between these forms of ephedrine. The scheduling of ephedrine in this manner will place a tremendous burden on those agencies responsible for administering international drug control. Ephedrine is regulated under the 1988 Convention and is defined only in relation to the term "ephedrine" and salts of ephedrine. See 1988 Convention, Annex. As such, current commercial documents pertaining to the export, import and distribution of precursor chemicals proposal would not likely list the products by their isomers. These documents form the basis for records and reports provided to the

International Narcotics Control Board ("INCB"). Therefore, the INCB is unlikely to receive accurate information or reports for scheduled versus unscheduled products containing ephedrine.

Scheduling only two isomers of ephedrine would also create problems for law enforcement. It will be extremely difficult if not impossible for law enforcement to distinguish between scheduled ephedrine and non-scheduled ephedrine in seizure situations. It is too much of a burden to expect customs and police officials to be able to distinguish between ephedrine isomers. Responsibility under the 1971 Convention is a matter for national authorities, while in Europe, for example, the responsibility for the 1988 Convention rests with the European Union. Reconciling the requirement of two bureaucracies will be extremely difficult. To avoid enormous confusion that will make enforcement impossible, ephedrine should continue to be regulated under the 1988 Convention as contemplated by the member countries to this convention.

B. WHO Acknowledges That Its Recommendation Will Create Overlapping Jurisdiction.

The WHO scheduling recommendation notes that "there are overlapping jurisdictions concerning the 1971 Convention and the [1988 Convention] which make full effective international regulations of ephedrine difficult." 64 Fed. Reg. at 1630. WHO states that this issue needs to be clarified by the appropriate international bodies. In fact, we have been informed that on January 28, 1999, WHO developed a proposal to resolve these jurisdictional issues. See WHO, Technical and Health Matters; Revised Guidelines for the WHO Review of Dependence-Producing Psychoactive Substances for International Control, EB103, Conf. Paper No. 7 (Jan. 28, 19999) (included as Appendix F). However, this proposal is unlikely to be implemented until sometime in 2000 and will have no impact on the confusion raised by the current WHO recommendation. This is yet another example of WHO's failure to provide adequate notice and discussion on international drug control issues affecting the public.

VI. International Scheduling Will Undermine Important U.S. Laws And Policy on Regulation of Ephedrine.

International scheduling of ephedrine will overturn several U.S. laws and nullify many important policies on OTC drug products and dietary supplements. In the ten years since signing the 1988 Convention, the United States has enacted three laws to regulate the distribution of listed chemicals: the Chemical Diversion Control Act of 1988, the Domestic Chemical Diversion and Control Act of 1993 and the Comprehensive Methamphetamine Control Act of 1996. In passing these laws, Congress carefully balanced the need to regulate these substances while ensuring that consumers would continue to have access to safe and cost effective products. Scheduling of ephedrine and enforcing the applicable requirement for prescriptions will nullify these laws and render meaningless a decade of

well-reasoned policy. DEA has also recently proposed to provide exemptions for certain ephedrine chemical mixtures in order to relieve the regulatory burden on distributors of dietary supplement and other products. International scheduling would revoke these regulations to the determinant of U.S. industry and consumers.

The WHO Recommendation to schedule ephedrine would overturn important provisions of the Dietary Supplement Health and Education Act of 1994. Given the lack of evidence supporting the international scheduling, such a result is an unconscionable rebuke of U.S. law. Similarly, the ongoing public debate over FDA's proposed rules on the OTC monograph (July 27, 1995) and to regulate dietary supplements containing ephedrine alkaloids (June 4, 1997) would be discarded. The United States cannot allow WHO and the CND to dictate bad policy that nullifies U.S. law and circumvents important policy debates in the United States, especially given the devastating effect on the millions of consumers who rely on OTC drug products and dietary supplements for health and well being.

VII. WHO and FDA Have Deprived Interested Parties of the Opportunity Comment.

In accordance with the 1971 Convention, WHO generally transmits scheduling recommendations to the Parties to the 1971 Convention to allow the Parties an opportunity to review the data and provide comments to the CND. See, e.g., 64 Fed. Reg. at 1629-30 (reprinting the WHO recommendation to schedule ephedrine). The CND subsequently considers the comments provided by the Parties to determine whether it will accept the WHO scheduling recommendation. Cf. 1971 Convention, art. 2, para. 5 (noting that the CND "may seek further information from . . . other appropriate sources"). The Parties' substantive review and comments have historically been a critical part of the CND deliberation on scheduling actions. By failing to follow its own guidelines regarding the publication of its critical review data, WHO has critically undermined the member States' ability to provide meaningful input into the international scheduling process. FDA has further compromised the ability of interested parties to contribute to the U.S. position on the international scheduling of ephedrine by failing to promptly publish the WHO recommendation, and by failing to make available important FDA and WHO technical documents.

A. By Failing to Adhere to its Own Internal Guidelines, WHO Compromised the Ability of the Parties to the 1971 Convention to Comment on the International Scheduling Process.

WHO has adopted guidelines to promote "principles of openness and transparency" and to ensure that "the information collected is generally made available for publication, particularly information contained in the report of the [ECDD]." WHO, Revised Guidelines for the WHO Review of Dependence-Producing Psychoactive Substances for International Control, PND/90.1 at 3, para. 8 (included as Appendix G). The WHO

guideline also states that WHO will provide copies of its scheduling recommendation and its critical review of the relevant scientific information to the Parties "in good time prior to the CND decision on international control." Id. at 3, para. 6. Perhaps most important, the guideline explains that "[t]he procedure has been designed to give ample time for governments to study the WHO recommendations and their justification prior to the session of CND." Id. at 3, para. 7. In this case, however, WHO has failed to adhere to its principles of openness and transparency by unnecessarily rushing the document through the international scheduling process.

To ensure that the Parties to the 1971 Convention are afforded ample time to participate in the international scheduling process, the WHO guideline establishes a time schedule of events to occur in the scheduling process. See id. at 16, app. 2. The critical steps in WHO scheduling process and an estimate of the key dates on the ephedrine recommendations are summarized in the following table:

Time Schedule for the WHO Scheduling Process		
Event	Guideline Schedule	Actual Schedule
1. Ongoing Information Collection	Year 1	October 14-18, 1996 (publicized in 1998). See WHO Technical Report Series No. 873, at 44 (1998) (recommending ephedrine for critical review) (included as Appendix H).
2. Selection for Critical Review	Year 2, March – April	December 30, 1997. See 63 Fed. Reg. 13,258, 13,258 (Mar. 18, 1998) (reprinting WHO questionnaire).
3. Critical Review Finished	Year 2, November – December	June 1998.
4. Circulation of Critical Review Document To Relevant Collaborating Information Sources	Year 2, December – Year 3, January	Inapplicable.
5. ECDD Assessment and Recommendations	Year 3, March – April	June 23-26, 1998. See 64 Fed. Reg. at 1629 (reprinting WHO scheduling recommendation).

Time Schedule for the WHO Scheduling Process		
Event	Guideline Schedule	Actual Schedule
6. ECDD Recommendation Submitted to the United Nations Secretary-General	Year 3, May – June	September 30, 1998. See 64 Fed. Reg. at 1629.
7. Circulation of WHO Recommendation to Parties to the 1971 Convention	Year 3, July – December	November 11, 1998. See 64 Fed. Reg. at 1630.
8. Decision on International Control	Year 4, February	March 1999. See 64 Fed. Reg. at 1629.

An analysis of the above table indicates that WHO failed to adhere to its internal guidelines at two crucial steps in the scheduling process. At the outset, WHO failed to provide public notice of its October 1996 recommendation to consider ephedrine for critical review until the publication nearly one and a half years later in the booklet summarizing its 30th meeting. Accordingly, the Parties and concerned public to the 1971 Convention were deprived of an opportunity to participate in the initial stages of the information collection for the critical review process.

The second major breakdown in the critical review process was WHO's failure to appropriately circulate the finished critical review prior to the June 1998 ECDD meeting. Had WHO complied with its procedural guideline, the Parties to the 1971 Convention would have had an opportunity to point out the errors in the WHO critical review document. WHO's failure to circulate the critical review document resulted in an ECDD scheduling recommendation that is based on flawed technical and scientific data.

WHO also violated its principles of openness and transparency by allowing the ECDD to consider technical data submitted by one of its members during the meeting. The document, which was described as pivotal by meeting observers, contained examples of ephedrine diversion in certain African countries gathered by the INCB under the 1998 Convention. See Background Paper for Dr. Cortes-Maramba (included as Appendix E). Despite the fact that this information was not subject to scientific and technical review by the WHO Secretariat, the information contained in this document undoubtedly helped persuade the ECDD to recommend international scheduling for ephedrine, as indicated by the references to African diversion problems in the recommendation notice. See 64 Fed. Reg. at 1630.

FDA and the U.S. Delegation must not endorse WHO's disregard for its own notions of openness and transparency. Rather, FDA should require WHO to adhere to its internal

guidelines to ensure that the international scheduling process is not based on inadequate technical and scientific data.

B. FDA Has Failed to Provide A Meaningful Opportunity to Comment on WHO's Recommendation to the CND.

The CSA provides that whenever the U.S. Secretary of State receives notice that the CND intends to consider a WHO scheduling recommendation, "the Secretary of State shall transmit timely notice to the Secretary of [Health and Human Services] who shall publish a summary of such information in the Federal Register and provide opportunity to interested persons to submit to him comments respecting the recommendation which he is to furnish . . . respecting such proposal." CSA § 201(d)(2)(B), 21 U.S.C. § 811(d)(2)(B) (emphasis added). In this case, the Secretary-General of the United Nations transmitted the WHO scheduling recommendation to the Secretary of State on, or shortly after, November 11, 1998. See 64 Fed. Reg. at 1629 (reprinting transmission notice). "In order to assist the [CND] in reaching a decision," the transmission notice requested that the U.S. government submit comments to the CND "at the latest by 4 January 1999." Id. at 1629-30.

However, FDA did not publish the WHO recommendation in the Federal Register until January 11, 1999 – one week after the CND deadline for comments. Further, FDA's late publication of the WHO scheduling recommendation severely limited interested parties' opportunity for comment, resulting in a comment period of less than 30 days. While we acknowledge that FDA's timeframes have been dictated in part by the relatively late notice provided by WHO, it is now obvious that FDA will not have sufficient time to review and evaluate the public comments prior to the March 1999 CND meeting.

This problem is compounded by the uncertainty expressed by FDA and affected industry about the scope and content of the WHO recommendation. For example, our conversations with officers from WHO and FDA indicate that it is unclear whether OTC drug products or dietary supplements may be exempted from scheduling as "exempt preparations." These same officials are uncertain whether dietary supplements containing Ephedra extracts are included in the WHO recommendation. Finally, WHO officials have stated that they recognize that it might be difficult or impossible for member countries to implement the requirements for scheduling. See 64 Fed. Reg. at 1630 (noting that the overlapping jurisdiction of the 1971 Convention and the 1988 Convention may lead to implementation problems). However, WHO has left no time for a discussion of the issues prior to CND consideration of the scheduling issue.

FDA has compounded the problems associated with the shortened review period by failing to make available essential WHO and FDA documents. By working with FDA, we were eventually able to obtain the portions of the information that FDA submitted in response to the WHO questionnaire. Other affected parties have not been so fortunate, as much of FDA's response to the WHO questionnaire was not placed into the WHO

scheduling docket until February 2, 1999. Although FDA informally provided us with copies of the SRS data that FDA submitted in support of its response to the WHO questionnaire, it is important to note that this information has yet to be placed in the WHO scheduling docket. Most important, although FDA possessed a copy of the WHO Critical Review Document – perhaps the single most important document for purposes of providing meaningful comment – FDA failed to place the critical review document in the docket.

Thus, because FDA failed to publish the WHO scheduling recommendation in a timely manner, and because the agency failed to make important WHO and FDA documents available for public inspection, the interested public has been deprived of its opportunity to submit meaningful comments.

As a result, it is incumbent on FDA and the U.S. Delegation to the CND to act immediately to make certain that the CND does not vote to schedule ephedrine and, at a minimum, request the CND to postpone any decision on scheduling ephedrine until the member countries have had the opportunity to review all the information available.

VIII. The Implications for U.S. Due Process.

Congress, industry, the public, FDA and DEA have worked hard for more than a decade to assure that drug control issues and safety issues pertaining to OTC drugs and dietary supplements containing ephedrine are handled in a fair and scientific manner. The legislative and rulemaking processes in the United States have served to protect and balance these important issues. Millions of dollars have been spent in this process, and billions of dollars of individual incomes and product sales have been at stake.

Of equal importance is the international drug control effort, which this country supports vigorously with the backing of affected U.S. commercial interests. American business sees the international drug control efforts as benign, and certainly not as a threat to the processes that guarantee fair play in the regulatory activities of FDA and DEA. The ill-timed, unwise scheduling effort under consideration could change this perception, because it undermines the regulatory processes underway with FDA and DEA. To threaten the interests of the regulated industry in this manner can make it an adversary to continued participation in the international efforts currently mandated by the Conventions.

FDA is not a helpless observer to this scheduling fiasco. The agency should have been more careful in the presentation of data when WHO called for it, and should have anticipated and warned WHO about the adverse effect of going forward, most particularly when the data are so lacking. And now FDA should take a leadership role to assure that the process does not go forward. If FDA simply allows events to flow towards an unjust, unwarranted scheduling, then it will be necessary for the affected parties to demand that Congress undertake a full, critical review of the way the United States

government participates in the Conventions' work, and whether this country can continue to take the kind of role it has had in the past.

IX. Conclusion.

The record comprising the WHO recommendation on scheduling of ephedrine, including the WHO Critical Review Document as supplemented by information from over 50 member countries, establishes that there is no abuse of dietary supplements containing Ephedra extracts and only anecdotal and inconclusive data on any type of ephedrine. The United States and other member countries must not permit scheduling of ephedrine to occur.

Given the negative consequences that scheduling ephedrine would have on continuing drug control efforts, FDA and the State Department must act now to contact other CND members to prevent scheduling. The CND should reject the WHO recommendation based on the lack of factual data to meet the criteria for scheduling under the 1971 Convention.

Respectfully submitted,

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The following documents are attachments to this comment and may be viewed at:

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

The Public Reading Room is open 9:00 am - 4:00 pm Monday through Friday except for Federal Holidays.

1. Edgar H Adams, Sc.D. Curriculum Vitae
2. "Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care," ed. Cooper, James R. MD, et al *NIDA Research Monograph 131, 1993., US Dept. of Health, Public Health Service, National Institute of Health.*
3. Drugs Included in Reimateimephed - printout
4. "Midwest Methamphetamine Working Group - Regional Strategy."

A. Statement of Edgar H. Adams, M.S., Sc.D.
B. Questionnaire for Data Collection for use by the World Health Organization and the Commission on Narcotic Drugs of the Economic and Social Council
C. Warning Letter dated August 29, 1997 to Sean S. Shayan, Global World Media Corp.
D. Ephedrin, ANNEX 2
E. "Background Paper for Dr. Cortes Marambe *Ephedring hydrochloride problems in African countries.*"
F. "Technical and health matters, Revised guidelines for the WHO review of dependence-producing psychoactive substances for international control, (Amendments proposed by Dr. J. Boufford, (United States of America) to the draft decision, amending decision EB93(16, as contained in document EB103/24)" 103rd Session, Agenda Item 3, EB103/Conf. Paper No. 7, January 28, 1999.
G. "WHO Technical Report Series 873, WHO Expert Committee on Drug Dependence" Thirtieth Report